Adding GLP-1 Receptor Agonist Therapy to Basal Insulin for Postprandial Glucose Control

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DOI: 10.2337/diaclin.33.2.73

Even with current guidelines, treatment algorithms, and recommendations available regarding diabetes management (1,2), providers struggle with adding therapies to manage postprandial hyperglycemia after basal insulin therapy in combination with oral antidiabetic medications (OADs) has failed to control a patient's hyperglycemia. Historically, after titration of basal insulin to achieve morning glucose control, adding a bolus, or prandial, rapid-acting insulin analog has been recommended either in a stepwise approach or as a full basal-bolus insulin regimen (3–5). However, recent research has shown that adding a GLP-1 receptor agonist to basal insulin may be as effective as adding prandial insulin therapy (6–8). These results have given providers and patients a potentially easier option when glycemic control is not achieved with basal insulin in combination with OADs. This article summarizes three recent articles demonstrating the glycemic control efficacy and other benefits of adding a GLP-1 receptor agonist to basal insulin and describes a strategy to implement this therapy in busy primary care settings.

Studies

Article A. Rosenstock J, Fonseca VA, Gross JL, et al.; Harmony 6 Study Group. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. Diabetes Care 2014;37:2317–2325

Article B. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet 2014;384:2228–2234

Article C. Diamont M, Nauck MA, Shaginian R, et al.; 4B Study Group. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care 2014;37:2763–2773

Summary

Article A reported on a randomized, open-label, active-controlled trial testing once-weekly albiglutide versus thrice-daily prandial insulin lispro as an add-on to titrated insulin glargine. The primary endpoint of the study was A1C change from baseline to 26 weeks. Albiglutide was found to be noninferior based on predefined endpoints but numerically superior to lispro as part of a basal-bolus insulin regimen, with A1C reductions of 0.82 and 0.66%, respectively. The albiglutide treatment group had a mean weight loss of 0.73 kg with no severe hypoglycemia and 15.8% rate of documented hypoglycemia. The lispro group had a mean 0.81 kg weight gain, two episodes of severe hypoglycemia, and a 29.9% rate of documented hypoglycemia. However, gastroin-

testinal side effects such as nausea, vomiting, and diarrhea were more common in the albiglutide group.

In article B, the authors reviewed studies comparing GLP-1 receptor agonist and basal insulin combination therapy to other antidiabetic therapy regimens. The main endpoints evaluated were glycemic control, hypoglycemia, and changes in weight. In all three endpoints, GLP-1 receptor agonist therapy was found to be superior to the other therapies studied, demonstrating robust glycemic control with no increases in the rate of hypoglycemia or weight gain. However, GLP-1 receptor agonist therapy was again associated with more gastrointestinal side effects than prandial insulin therapy.

Article C reported on a 30-week, open-label, multicenter, randomized, noninferiority trial comparing exenatide to thrice-daily lispro added to a background of glargine and metformin. The primary endpoint was A1C change from baseline to 30 weeks. Exenatide was found to be noninferior to lispro based on predefined endpoints as part of a basal-bolus insulin regimen. A1C reductions were 1.13% with exenatide and 1.10% with lispro. The exenatide treatment group had a mean weight loss of 2.5 kg, two episodes of severe hypoglycemia, and a 30% incidence of minor hypoglycemia, whereas the lispro group had a mean weight gain of 2.1 kg, seven episodes of severe hypoglycemia, and a 41% incidence of minor hypoglycemia. Gastrointestinal side effects were more common in the exenatide group.

Commentary

These three articles help to reinforce the potential benefits of GLP-1 receptor agonist therapy (6). Such benefits include:

- Glucose-dependent insulin secretion
- Glucose-dependent glucagon secretion
- Low risk of hypoglycemia
- Possible weight loss
- Postprandial glucose control
- Less energy intake
- Increased satiety
- Delayed gastric emptying

Beyond these potential pharmacological benefits are two additional advantages: *1*) less of a treatment burden for patients resulting from fewer required injections compared to a basal-bolus insulin regimen and *2*) easier patient education and simplified dose titration for providers initiating GLP-1 receptor agonist treatment compared to rapid-acting prandial insulin.

Important indications, warnings, and contraindications regarding GLP-1 receptor agonist therapy (7–11) include:

- Contraindicated (with the exception of exenatide) in patients with a personal or family history of medullary thyroid carcinoma
- Contraindicated (with the exception of exenatide) in those with a history of multiple endocrine neoplasia syndrome type 2
- To be used with caution in patients with a history of pancreatitis or gastroparesis
- Not to be used (with the exception of dulaglutide) in patients using prandial insulin
- Not for use in patients with type 1 diabetes
- Not for use in patients with diabetic ketoacidosis
- May cause hypersensitivity reactions
- Dulaglutide and once-weekly exenatide, at the time of publication, did not have a Food and Drug Administration–approved indication for use with basal insulin

Translating this recent important research into practice will give providers and their patients with type 2 diabetes an alternative when prandial insulin is thought to be an excessive treatment burden for the patient, an educational burden for the provider, or a regimen beyond the provider's level of comfort or expertise. These articles provide evidence in support of the hypothesis that the benefits of GLP-1 receptor agonist therapy outweigh the associated risks. The most efficacious use of a GLP-1 receptor agonist would be in patients whose A1C level is within 1–1.5 percentage points from their individualized target. Patients whose A1C is >1.5 percentage points above target likely will gain more benefit from aggressive insulin management strategies when oral therapies and basal insulin have failed to provide adequate glycemic control.

Implementing this new treatment option in a busy primary care office should be a fairly simple process involving the following steps:

1. Identify as possible candidates patients who are not at their A1C target despite taking OAD(s) and >0.5–0.7 units/kg of basal insulin or taking basal insulin appropriately titrated to morning glucose control.
2. Be sure the patient is within 1–1.5 percentage points of his or her A1C target for the best chance of success.
3. Discuss the proposed therapy with the patient to be sure none of the warnings, precautions, or contraindications listed above preclude its initiation.
4. Find out which of the available GLP-1 receptor agonists are covered by the patient's insurance plan.
5. Discuss with the patient the most common potential side effects such as nausea, vomiting, and allergic reactions.
6. Encourage the patient to regularly self-monitor his or her blood glucose and log the results.
7. Teach the patient proper injection technique and proper dosing; this should be carried out by the provider, a nurse or medical assistant in the provider's office, or the patient's pharmacist.

8. Arrange a follow-up visit in ~1 month to evaluate treatment efficacy and assess the patient for possible side effects.

Following these steps should allow primary care providers to help appropriate patients achieve improved glycemic control, weight loss, and a reduced risk of hypoglycemia—the trifecta of successful diabetes management.

Duality of Interest

The author serves as a speaker, consultant, and/or advisor to AstraZeneca, Boehringer Ingelheim, Eli Lilly and Co., Janssen Pharmaceuticals, Forest Pharmaceuticals, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: a position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379

2. Garber AJ, Abrahamson MJ, Barzilay JI, et al.; American Association of Clinical Endocrinologists. AACE comprehensive diabetes management algorithm 2013. Endocr Pract 2013;19:327–336

3. Rodbard HW, Visco VE, Andersen H, Hiort LC, Shu DHW. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP study): a randomised, treat-to-target clinical trial. Lancet Diabetes Endocrinol 2014;2:30–37

4. Lankisch MR, Ferlinz KC, Leahy JL, Scherbaum WA; Orals Plus Apidra and Lantus (OPAL) study group. Introducing a simplified approach to insulin therapy in type 2 diabetes: a comparison of two single-dose regimens of insulin glulisine plus insulin glargine and oral antidiabetic drugs. Diabetes Obes Metab 2008;10:1178–1185

5. Davidson MB, Raskin P, Tanenberg RJ, Vlajnic A, Hollander P. A stepwise approach to insulin therapy in patients with type 2 diabetes mellitus and basal insulin treatment failure. Endocr Pract 2011;17:395–403

6. Bloomgarden ZT, Blonde L, Garber AJ, Wysham CH. Current issues in GLP-1 receptor agonist therapy for type 2 diabetes. Endocr Pract 2012;18 (Suppl. 3):6–26

7. Victoza package insert. Plainsboro, NJ, Novo Nordisk, April 2013

8. Byetta package insert. Wilmington, Del., AstraZeneca Pharmaceuticals, August 2014

9. Tanzeum package insert. Wilmington, Del., GlaxoSmithKline, June 2014

10. Bydureon package insert. Wilmington, Del., AstraZeneca Pharmaceuticals, October 2014

11. Trulicity package insert. Indianapolis, Ind., Eli Lilly and Co., September 2014